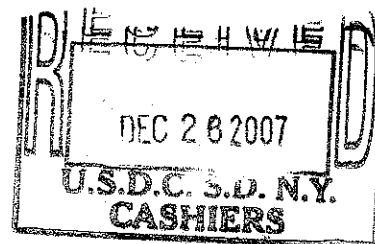


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JUDGE KOELTL

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

07 CV 11614

Mitsubishi Chemical Corporation,
Mitsubishi Tanabe Pharma Corporation,
Encysive Pharmaceuticals Inc., SmithKline
Beecham plc and SmithKlineBeecham Corp.
d/b/a GlaxoSmithKline,

Plaintiffs,

v.

Barr Laboratories, Inc.,

Defendant.

Civil Action No. _____

COMPLAINT

Plaintiffs, Mitsubishi Chemical Corporation (“MCC”), Mitsubishi Tanabe Pharma Corporation (“MTPC”), Encysive Pharmaceuticals Inc. (“Encysive”), SmithKline Beecham plc and SmithKline Beecham Corp. d/b/a GlaxoSmithKline (collectively, “GSK”) (collectively, “Plaintiffs”), by their undersigned counsel, for their Complaint against defendant Barr Laboratories, Inc. (“Barr”) allege as follows:

Jurisdiction and Venue

1. This is an action for patent infringement arising under the patent laws of the United States, Title 35, United States Code, and arising under 35 U.S.C. §§ 271(e)(2), 271(b), 271(c) and 281-283. Subject matter jurisdiction is proper under 28 U.S.C. §§ 1331 and 1338(a). Venue is proper under 28 U.S.C. §§ 1391(b)-(d) and 1400(b). Personal jurisdiction over the Defendant in New York is proper under N.Y. C.P.L.R. §§ 301 and 302(a).

The Parties

2. MCC is a Japanese corporation having its corporate headquarters and principal place of business in Tokyo, Japan. MCC is engaged in the business of employing the science of chemistry to create, develop, and improve products with a particular focus in the areas of petrochemicals, performance and functional products, and health care.

3. MTPC is a Japanese corporation having its corporate headquarters and principal place of business in Osaka, Japan. MTPC is a pharmaceutical company that engages in the development, manufacture, and marketing of a broad spectrum of innovative pharmaceutical products.

4. Encysive is a Delaware corporation having its corporate headquarters and principal place of business in Houston, Texas. Encysive is a biopharmaceutical company engaged in the discovery, development, and commercialization of novel compounds to address unmet medical needs.

5. SmithKline Beecham plc is an English company having its registered office in Brentford, England. SmithKline Beecham Corp. is a Pennsylvania corporation having a principal place of business at One Franklin Plaza, Philadelphia, Pennsylvania. GSK is a research-based pharmaceutical company.

6. Upon information and belief, Barr is a Delaware corporation with its corporate headquarters in Pomona, New York. Barr is in the business of manufacturing and marketing generic pharmaceuticals. Upon information and belief, Abbreviated New Drug Application (“ANDA”) No. 79-238 was filed under the name of Barr. Upon information and belief, Barr derives substantial revenue from interstate and/or international commerce. Upon information and belief, Barr does business in the Southern District of New York and, by filing ANDA No. 79-238, has committed a tortious act outside the state of New York that Barr expects or should reasonably expect to have consequences in the state. Barr is registered with the New York Department of State, Division of Corporations, to do business in New York as a foreign corporation.

7. United States Patent No. 5,214,052 (“the ’052 Patent”), entitled “Method for Dissolving Arginineamides and Pharmaceutical Compositions Containing Them”, a true and correct copy of which is appended hereto as Exhibit A, was duly issued on May 25, 1993 to inventors Kunihiro Ofuchi and Tatsuo Nomura, and assigned to MCC (then known as Mitsubishi Kasei Corporation). The ’052 Patent claims, *inter alia*, a novel

injectable pharmaceutical composition comprising 1-[5-[(aminoiminomethyl)amino]-1-oxo-2-[[[(1,2,3,4-tetrahydro-3-methyl-8-quinoliny)lsulfonyl]amino]pentyl]-4-methyl-2-piperidinecarboxylic acid, monohydrate (“Argatroban”) dissolved in a solvent containing ethanol, water, and a saccharide (“Argatroban Injection”) as well as the method of preparation of Argatroban Injection.

8. MCC has been and is the owner of the '052 Patent which expires on June 30, 2014, having received a patent term extension pursuant to 35 U.S.C. § 156.

9. MTPC is the successor in interest to certain rights in MCC's pharmaceutical business including rights relating to Argatroban Injection, and holds an exclusive license to the '052 Patent with the right to sublicense, as well as certain rights under a license agreement relating to Argatroban Injection between MCC and Encysive.

10. Encysive holds an exclusive sublicense to the '052 Patent for the United States territory. Encysive's exclusive sublicense includes the right to further sublicense. Encysive is also the holder of the approved new drug application (“NDA”) for Argatroban Injection.

11. GSK is the exclusive sublicensee of Encysive and is the sole distributor of Argatroban Injection in the United States.

12. Plaintiffs will be both substantially and irreparably harmed by infringement of the '052 Patent. There is no adequate remedy at law.

The New Drug Application

13. GSK sells Argatroban Injection in the United States pursuant to the United States Food and Drug Administration's approval of an NDA held by Encysive. The NDA for Argatroban Injection, NDA No. 020883, was approved on June 30, 2000.

14. Argatroban Injection is an anticoagulant that is approved for use including prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia.

COUNT I
(DIRECT INFRINGEMENT OF U.S. PATENT NO. 5,214,052 UNDER
35 U.S.C. § 271(e)(2)(A) BY DEFENDANT)

15. Plaintiffs repeat and incorporate herein by reference the allegations contained in paragraphs 1 through 14 above.

16. Upon information and belief, defendant Barr filed ANDA No. 79-238 with the Food and Drug Administration ("FDA") under 21 U.S.C. § 355(j) seeking approval to market generic Argatroban Injection.

17. By this ANDA filing, Defendant has indicated that it intends to engage in, and that there is substantial likelihood that it will engage in, the commercial manufacture, use, offer for sale, sale, and/or importation of the patented product immediately or imminently upon receiving FDA approval to do so. Also by Barr's ANDA filing, Barr has indicated that the drug product for which it seeks FDA approval (the "Proposed Product") is bioequivalent to Argatroban Injection.

18. By this ANDA filing, Barr seeks to obtain approval to commercially manufacture, use, offer for sale, sell, and/or import alleged generic equivalents of Argatroban Injection prior to the expiration date of the '052 Patent.

19. By a letter dated November 16, 2007 (the "Letter"), Barr informed Plaintiffs that it had filed a certification to the FDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV). On or about November 19, 2007, patent owner MCC received a copy of the Letter. On or about November 19, 2007, NDA holder Encysive received a copy of the Letter.

20. The Letter, purporting to be Barr's Notice of Certification under 21 U.S.C. § 355(j)(2)(B), alleges that, in Barr's opinion, "the '052 patent is invalid, unenforceable, or will not be infringed by the manufacture, importation, use or sale of the drug product described in Barr's ANDA."

21. Barr asserts that claims 1 – 4 of the '052 Patent are invalid under 35 U.S.C. § 103(a) in view of two references: Yoshikuni Tamao *et al.*, "Alpha-(N-arylsulfonyl-L-argininamides, Processes for Their Preparation and Pharmaceutical Composition Containing These Substances," European Patent Application No. 79103092.7, and George M. Krause and John M. Cross, "Solubility of Phenobarbital in Alcohol-Glycerin-Water Systems," *Journal of the American Pharmaceutical Association*, Vol. XL:137-139 (1951).

22. The '052 Patent is not invalid under 35 U.S.C. § 103(a).

23. Beyond summarily claiming that "the '052 patent is invalid, unenforceable, and/or will not be infringed by" the Proposed Product, Barr does not specifically assert that the '052 Patent is unenforceable, and the Letter does not provide any factual or legal basis for an assertion that the '052 Patent is unenforceable, as required by applicable law.

24. Beyond summarily claiming that "the '052 patent is invalid, unenforceable, and/or will not be infringed by" the Proposed Product, Barr does not specifically assert that the drug product for which it seeks approval would not infringe the '052 Patent, and the Letter does not provide any factual or legal basis for an assertion that the drug product for which Barr seeks approval would not infringe the '052 Patent, as required by applicable law.

25. Beyond summarily claiming that “any available objective evidence of nonobviousness is insufficient to rebut the *prima facie* case of obviousness,” Barr’s Letter does not provide any analysis of secondary considerations of nonobviousness. The Letter also fails to provide any factual or legal basis for Barr’s assertion that “any available objective evidence of nonobviousness is insufficient to rebut the *prima facie* case of obviousness,” as required by applicable law.

26. Barr’s filing of ANDA No. 79-238 for the purpose of obtaining FDA approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of a generic equivalent of Argatroban Injection before the expiration of the ’052 Patent is an act of infringement under 35 U.S.C. § 271(e)(2)(A).

27. Defendant’s manufacture, use, offer for sale, sale, and/or importation of the Proposed Product will directly infringe, upon information and belief, at least one of the claims of the ’052 Patent.

28. Unless Defendant is enjoined from infringing the ’052 Patent, Plaintiffs will suffer substantial and irreparable injury.

29. Plaintiffs have no adequate remedy at law.

COUNT II
**(INDUCEMENT OF INFRINGEMENT OF U.S. PATENT NO. 5,214,052
UNDER 35 U.S.C. § 271(b) BY DEFENDANT)**

30. Plaintiffs repeat and incorporate herein by reference the allegations contained in paragraphs 1 through 29 above.

31. Upon information and belief, sale of the Proposed Product will induce others to infringe the ’052 Patent.

32. Upon information and belief, Barr knows or reasonably should know that sale of the Proposed Product will induce others to infringe the ’052 Patent.

33. Upon information and belief, Barr specifically intends that others will use the Proposed Product to infringe the '052 Patent.

34. Unless Defendant is enjoined from inducing infringement of the '052 Patent, Plaintiffs will suffer substantial and irreparable injury.

35. Plaintiffs have no adequate remedy at law.

COUNT III
**(CONTRIBUTORY INFRINGEMENT OF U.S. PATENT NO. 5,214,052
UNDER 35 U.S.C. § 271(c) BY DEFENDANT)**

36. Plaintiffs repeat and incorporate herein by reference the allegations contained in paragraphs 1 through 35 above.

37. Upon information and belief, the Proposed Product constitutes a material part of the invention disclosed in the '052 Patent.

38. Upon information and belief, the Proposed Product will be especially made for use in an infringement of the '052 Patent.

39. Upon information and belief, Barr knows that the Proposed Product will be especially made for use in an infringement of the '052 Patent.

40. Upon information and belief, sale of the Proposed Product will result in direct infringement of the '052 Patent.

41. Upon information and belief, the Proposed Product is not a staple article or commodity of commerce which is suitable for substantial noninfringing use.

42. Upon information and belief, Barr knows that the Proposed Product is not a staple article or commodity of commerce which is suitable for substantial noninfringing use.

43. Unless Defendant is enjoined from contributorily infringing the '052 Patent, Plaintiffs will suffer substantial and irreparable injury.

44. Plaintiffs have no adequate remedy at law.

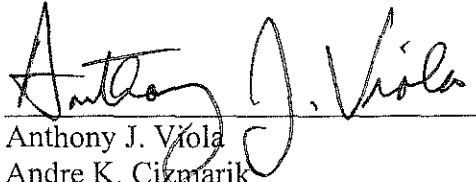
WHEREFORE, Plaintiffs request the following relief:

- (a) a judgment that making, using, selling, offering to sell and/or importing Defendant's drug product for which it seeks FDA approval will infringe, induce infringement of, and/or contributorily infringe at least one claim of the '052 Patent;
- (b) a declaratory judgment pursuant to 28 U.S.C. § 2201 et seq. that making, using, selling, offering to sell and/or importing Barr's drug product for which it seeks FDA approval will infringe, induce infringement of, and/or contributorily infringe at least one claim of the '052 Patent;
- (c) a judgment and order pursuant to 35 U.S.C. § 271(e)(4)(A) providing that the effective date of any FDA approval for Defendant to commercially make, use, sell, offer to sell or import Defendant's drug product for which it seeks FDA approval be no earlier than the date following the expiration date of the '052 Patent;
- (d) a permanent injunction restraining and enjoining against any infringement, inducement of infringement, or contributory infringement by Defendant, its officers, agents, attorneys, and employees and those acting in privity or concert with all or any of them, of the '052 Patent through the commercial manufacture, use, sale, offer for sale or

importation into the United States of Defendant's drug product for which it seeks FDA approval;

- (e) Attorneys' fees in this action under 35 U.S.C. § 285;
- (f) Such further and other relief as this Court may deem just and proper.

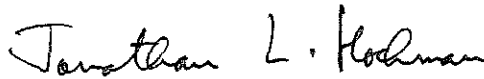
Dated: New York, N.Y.
December 27, 2007



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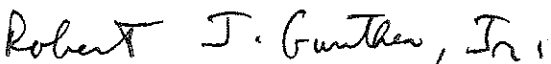
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EXHIBIT A

[45] Date of Patent: May 25, 1993

- 4 Claims, 3 Drawing Sheets**

U.S. Patent

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Sheet 1 of 3

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Fig. 1

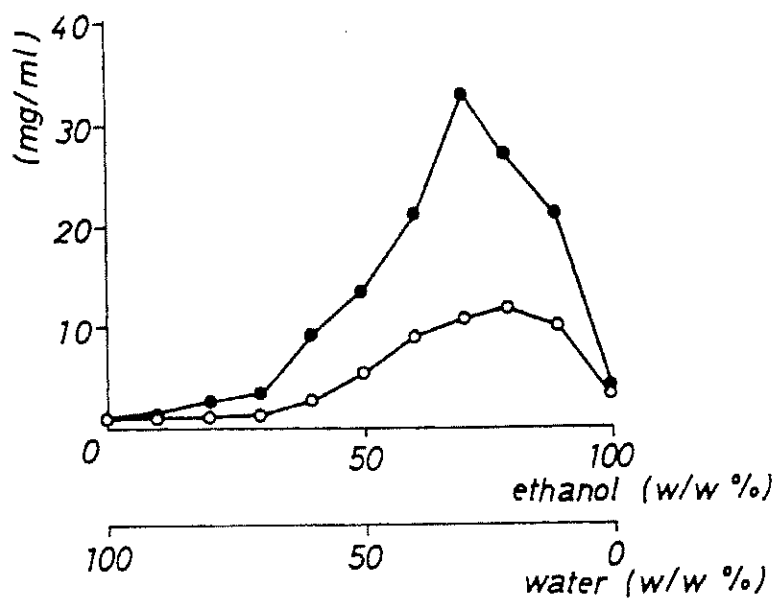
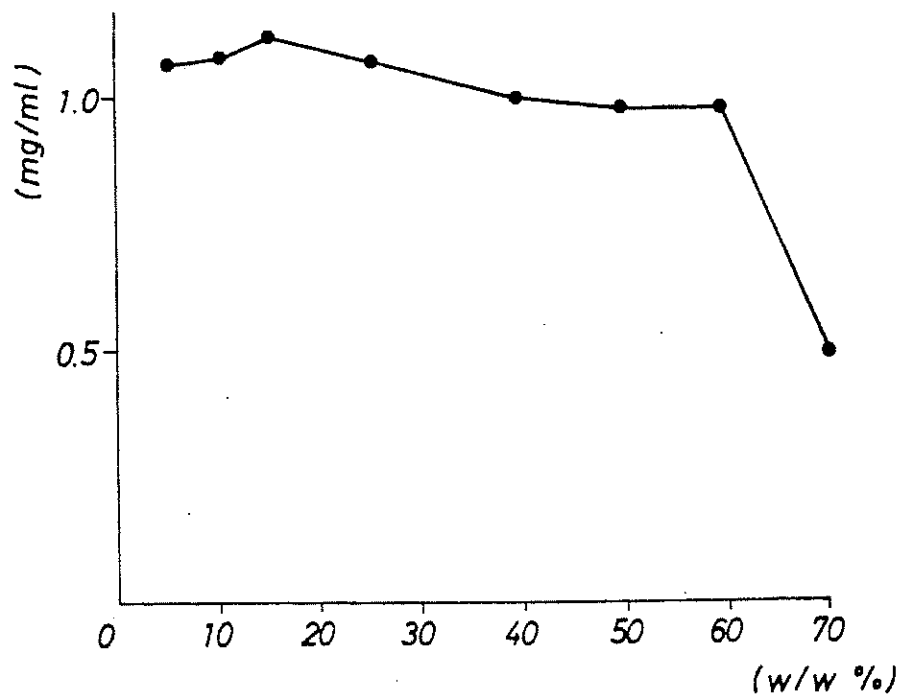


Fig. 2



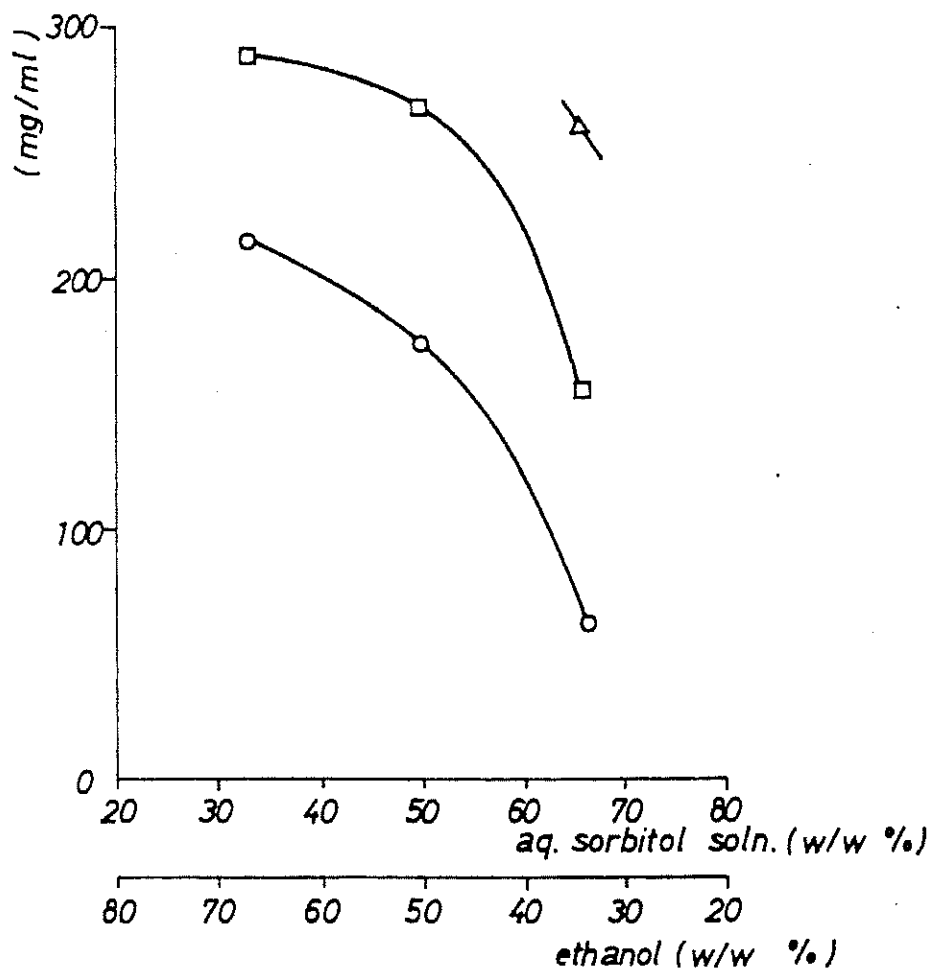
U.S. Patent

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Sheet 2 of 3

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Fig. 3



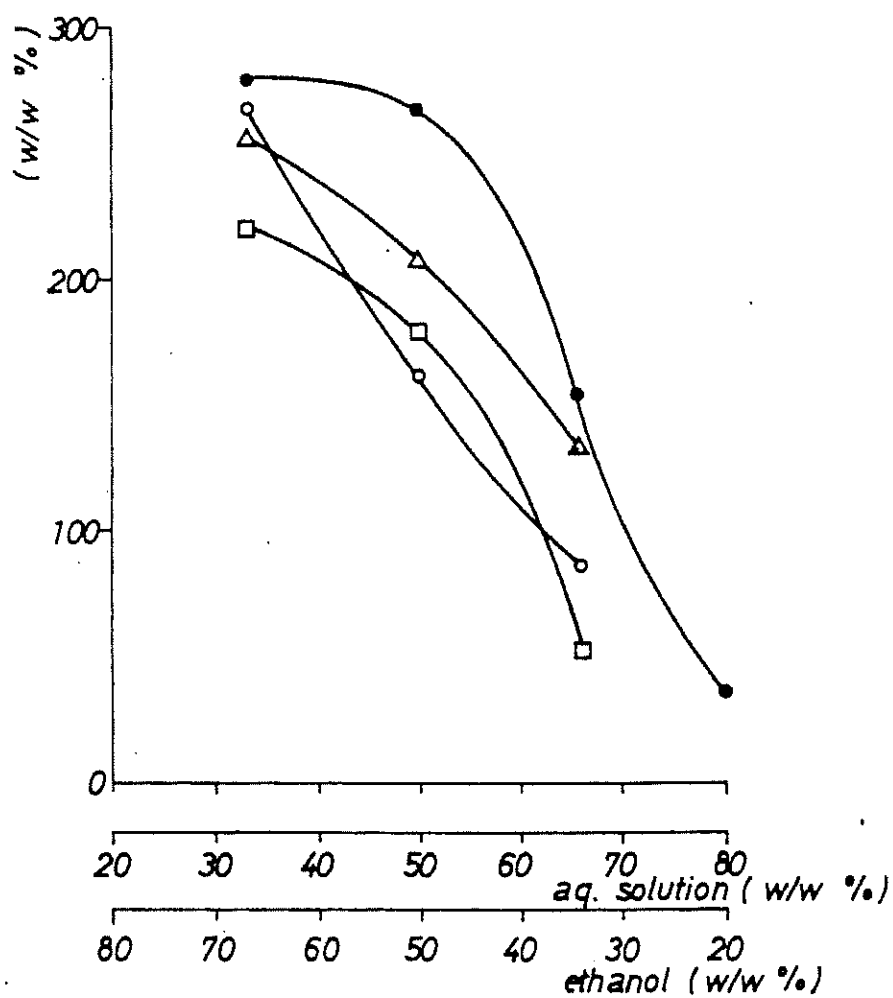
U.S. Patent

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Fig. 4



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METHOD FOR DISSOLVING ARGinineAMIDES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

This application is a continuation of application Ser. No. 07/577,042, filed on Aug. 30, 1990, now abandoned, which is a continuation of abandoned application Ser. No. 07/223,152 filed Jul. 22, 1988.

FIELD OF THE INVENTION

The invention relates to a method for dissolving arginineamides and pharmaceutical compositions containing them.

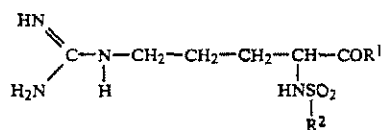
BACKGROUND OF THE INVENTION

Arginineamides are known to have anti-thrombotic activities and are expected to be used as anti-thrombotic agents (please refer to Japanese Patent No. 1382377). However, it is very difficult to obtain a solution containing any of arginineamides at high concentration due to poor solubility in water and therefore any of these compounds is not suitable for applying as the injection containing it at high concentration.

An object of the invention is to provide a method for improving the solubilities of arginineamides so as to apply as the injections containing them at high concentration.

SUMMARY OF THE INVENTION

The invention provides a method for dissolving arginineamide comprising dissolving N²-arylsulfonyl-L-arginineamide having the general formula (I)



wherein R¹ represents a (2R, 4R)-4-alkyl-2-carboxypiperidino group and R² represents a phenyl group or a condensed polycyclic compound residue which may be substituted with one or more substituents selected from lower alkyl groups, lower alkoxy groups and lower alkyl-substituted amino groups, said condensed polycyclic compound residue including a benzene ring which binds to sulfur atom of the sulfonyl group in the general formula (I) and is condensed with one or more other rings which may be heterocyclic and having 7 to 14 carbon atoms as the ring-constituent atoms;

and/or its salt in a solvent of alcohol and water. Further, the invention provides pharmaceutical compositions containing arginineamides.

BRIEF DESCRIPTION OF THE DRAWINGS

A more complete understanding of the invention and many of the attendant advantages thereof will be readily obtained as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying drawings, wherein:

FIG. 1 is a graph showing the solubility of argipidine in solvent (mg/ml) over a range of ethanol-water solvent mixture;

FIG. 2 shows the solubility of argipidine in aqueous sorbitol solution,

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FIG. 3 shows the solubility of argipidine over a range of ethanol-aqueous sorbitol solutions containing different amounts of sorbitol; and

FIG. 4 shows the solubility of argipidine over a range of ethanol-aqueous solutions, wherein the aqueous solutions contain glucose, glycerin, sorbitol or sucrose.

DETAILED DESCRIPTION OF THE INVENTION

R¹ in the general formula (I) represents a (2R, 4R)-4-alkyl-2-carboxypiperidino group. The alkyl herein is a lower alkyl having 1 to 5 carbon atoms such as methyl, ethyl, propyl, isopropyl and butyl. Preferably, R¹ represents a (2R, 4R)-4-methyl-2-carboxypiperidino group.

R² in the general formula (I) represents a phenyl group or a condensed polycyclic compound residue. The condensed polycyclic compound residue defines herein that it includes a benzene ring which binds to sulfur atom of the sulfonyl group in the general formula (I) and is condensed with one or more other rings which may be heterocyclic and it has 7 to 14 carbon atoms as the ring-constituent atoms. The benzene ring included in the condensed polycyclic compound residue binds to sulfur atom of the sulfonyl group in the general formula (I), provided that the position on the benzene ring binding to the sulfur atom is not particularly limited. A heteroatom or heteroatoms constituting the heterocyclic ring may be oxygen, nitrogen or sulfur atom.

Preferable condensed polycyclic compound residue is a dicyclic compound residue including benzene ring condensed with one other ring, preferably one five- or six-membered ring which may be heterocyclic or a tricyclic compound residue including benzene ring condensed with two other rings, preferably two five or six-membered rings which may be heterocyclic. The examples of such condensed polycyclic compound residues include anthryl, phenanthryl, benzofuranyl, dibenzothienyl, phenoxthieryl, quinolyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, benzimidazolyl, fluorenyl, 2,3-dihydrobenzofuranyl, thioxathienyl, naphthyl, tetrahydronaphthyl, isoquinolyl, tetrahydroquinolyl and tetrahydroisoquinolyl.

If desired, R² can be substituted with one or more substituents selected from lower alkyl groups, lower alkoxy groups and lower alkyl-substituted amino groups. The lower alkyl group is alkyl group having 1 to 5 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl and tert-butyl. The lower alkoxy group is alkoxy group having 1 to 5 carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy and butoxy. And, the lower alkyl-substituted amino group is the amino group substituted with the above-mentioned lower alkyl group, such as alkylamino and dialkylamino.

Preferably, R² represents 3-methyl-1,2,3,4-tetrahydro-8-quinolyl group.

As the arginineamides used in the invention, the following compounds are exemplified.

(2R, 4R)-1- [N²-(3-isopropoxybenzenesulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid;

(2R, 4R)-1- [N²-(3,5-dimethyl-4-propoxybenzenesulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid;

(2R, 4R)-1- [N²-(5,6,7,8-tetrahydro-2-naphthalenesulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid;

(2R, 4R)-1- [N²-(5-dimethylamino-1-naphthalenesulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid;

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(2R, 4R)-1-[N²-(3-methyl-1,2,3,4-tetrahydro-8-quinoline-sulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid;

(2R, 4R)-1-[N²-(2-dibenzothiophenesulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid;

(2R, 4R)-1-[N²-(2,4-dimethoxy-3-butoxybenzenesulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid;

(2R, 4R)-1-[N²-(3,5-dimethyl-4-propoxybenzenesulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid;

(2R, 4R)-1-[N²-(3-ethyl-1,2,3,4-tetrahydro-8-quinoline-sulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid;

(2R, 4R)-1-[N²-(2-carbazolesulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid;

(2R, 4R)-1-[N²-(2-fluorenesulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid;

(2R, 4R)-1-[N²-(2-phenoxthinesulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid;

(2R, 4R)-1-[N²-(2-anthracenesulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid; and

(2R, 4R)-1-[N²-(7-methyl-2-naphthalenesulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid; as well as their 4-ethyl analogues, their 4-propyl analogues, their 4-butyl analogues and their 4-pentyl analogues.

The invention can use the salts of arginineamides having the general formula (I). The salts may be acid addition salts prepared by reacting with any inorganic or organic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid, acetic acid, citric acid, maleic acid, succinic acid, lactic acid, tartaric acid, gluconic acid, benzoic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid and *p*-toluenesulfonic acid. Further, the salts may be inorganic or organic salts prepared by reacting organic or inorganic bases such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, triethylamine, procaine, dibenzylamine, N, N'-dibenzylethylenediamine and N-ethylpiperidine.

In the method for dissolving an arginineamide according to the invention, the arginineamide and/or its salt is dissolved in the solvent of alcohol and water. As the alcohols used in the invention, monohydric alcohols such as methanol, ethanol and the like; dihydric alcohols such as ethyleneglycol, propyleneglycol and the like; polyhydric alcohols such as glycerine and the like; and ethers of di- and polyhydric alcohols such as polyethyleneglycol and the like are mentioned. Methanol, ethanol, propyleneglycol and polyethyleneglycol are preferable. Ethanol is particularly preferable. If necessary, a mixture of these alcohols can be used.

Water used in the invention is generally distilled water or purified water, but a physiological saline or Ringer's solution may be used.

The mixed ratio (by weight) of alcohol to water in the above solvent is generally 0.1 to 10, preferably 0.2 to 5 and more preferably 0.3 to 3.

If necessary, any saccharides can be admixed with the solvent of alcohol and water in the invention. As the saccharides used in the invention, monosaccharides, oligosaccharides, polysaccharides and their reduced derivatives (for example sugaralcohol) which are soluble in water are mentioned. Among them, glucose, fructose, maltose, saccharose and D-sorbitol each of which has the high solubility in water are preferable. D-sorbitol is particularly preferable. A mixture of these saccharides may be used.

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The mixed ratio (by weight) of saccharide (if present) to water is generally 0.1 to 10, preferably 0.4 to 4 and more preferably 0.5 to 2.

The manner how to dissolve the arginineamide having the general formula (I) in the solvent of alcohol and water and optionally saccharide is not particularly limited. Generally, the saccharide is dissolved in water and then the alcohol is added thereto followed by mixing. Next, the arginineamide is slowly added while stirring until complete dissolution.

The temperature on dissolution is not particularly limited. When the saccharide is dissolved in water, however, it is preferable to war water at 40 to 70° C for accelerating the dissolution rate.

Further, when the volatile alcohol such as ethanol and the like is used, it is necessary to take care for preventing the evaporation of alcohol, for example by cooling the solution to room temperature before the dissolution, or dissolving in a closed container.

The concentration of arginineamide in the solution can be selected within the wide range depending on the intended uses. According to the invention, the solution in which the arginineamide is dissolved at high concentration, for example from several times to several thousands times the solubility of arginineamide in water can be obtained.

The solution containing any of the arginineamide having the general formula (I) in the solvent of alcohol and water and optionally saccharide thus obtained can constitute the pharmaceutical composition of the invention.

The pharmaceutical compositions of the invention are useful for treating thrombosis. Accordingly, the pharmaceutical compositions can be used as the anti-thrombotic agents.

The pharmaceutical composition of the invention may contain antiseptic, anti-oxidant, soothing agent, pH-controlling agent and the like. And, if necessary any pharmaceutical ingredient(S) other than the arginineamides may be added to form the combined preparation.

The pharmaceutical composition of the invention is injectable as the injection. This injectable composition may contain stabilizer, buffer, preservative and the like which are acceptable for the injection may be added in addition to the above-mentioned ingredients. If desired, the injectable composition according to the invention is prepared to contain the arginineamide at very high concentration, which is used by diluting with water, electrolyte, carbohydrate solution, Ringer's solution or the like on the application such as infusion and dialysis.

Alternatively, the pharmaceutical composition of the invention is topically applicable as the solution for topical application, the ointment or the suppository. When the pharmaceutical composition is used as the solution for topical application, the solution prepared above can be used as it is. And, the ointment or the suppository of the invention may be prepared by dissolving the solution prepared above in the base or the like.

EXAMPLES

The invention will now be further described by the following, non-limiting examples.

Example 1

(2R, 4R)-1-[N²-(3-methyl-1,2,3,4-tetrahydro-8-quinolinesulfonyl)-L-arginyl]-4-methyl-2-piperidinecarboxylic acid (argipidine) was dissolved in the solvent

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of ethanol and water while varying the mixed ratio of ethanol to water at 20° C. () or 5° C. (°).

The results are shown in FIG. 1. In FIG. 1, the ordinate is the solubility of argipidine in the solvent (mg/ml) and the abscissa is the weight percentages of ethanol and water (w/w %).

As shown in FIG. 1, the solubility of argipidine in the solvent comprising 70 % by weight of ethanol and 30 % by weight of water at 20° C. was 33.23 mg/ml and that at 5° C. was 10.73 mg/ml.

COMPARATIVE EXAMPLE 1

Argipidine was dissolved in the aqueous sorbitol solution while varying the sorbitol concentration at 20° C.

The result was shown in FIG. 2. In FIG. 2, the ordinate is the solubility of argipidine in the aqueous sorbitol solution (mg/ml) and the abscissa is the concentration of sorbitol in the aqueous solution (w/w %).

As shown in FIG. 2, the solubility of argipidine in the aqueous sorbitol solution was low and it was the substantially same as the solubility of argipidine in water.

EXAMPLE 2

Argipidine was dissolved in the solvent comprising the aqueous 25 % sorbitol solution (°), the aqueous 50 % sorbitol solution (□) or the 70 % sorbitol solution (Δ) and ethanol while varying the mixed ratio of ethanol to the aqueous sorbitol solution at 30° C.

The results are shown in FIG. 3. In FIG. 3, the ordinate is the solubility of argipidine in the solvent (mg/ml) and the abscissa is the weight percentages of the aqueous sorbitol solution and ethanol (w/w %).

EXAMPLE 3

Argipidine was dissolved in the solvent comprising the aqueous 33% glucose solution (°), the aqueous 50% glycerine solution (Δ), the 50% sorbitol solution () or the aqueous 50% sucrose solution (□) and ethanol while varying the mixed ratio of ethanol to the aqueous solution at 30° C.

The results are shown in FIG. 4. In FIG. 4, the ordinate is the solubility of argipidine in the solvent (mg/ml) and the abscissa is the weight percentages of the aqueous solution and ethanol (w/w %).

EXAMPLE 4

The distilled water for injection (200 g) was placed in a one-litre beaker, to which D-sorbitol (300 g) was added with stirring and dissolved. At this time, if necessary the solution may be heated. Then, ethanol (400 g) was added and mixed with stirring followed by adding argipidine (100 g) with stirring until complete dissolution.

The thus-obtained solution can be used for dialysis after diluting it with the weak acidic solution containing D-sorbitol.

EXAMPLE 5

The distilled water for injection (200 g) was placed in a one-litre beaker, to which glucose (200 g) was added with stirring and dissolved. Then, ethanol (400 g) was added and mixed with stirring followed by adding argipidine (100 g) with stirring. Further, the distilled water for injection was added till the total volume of the solution became 1 litre.

The thus-obtained solution can be used for drip infusion after diluting it with the aqueous sorbitol solution,

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the aqueous D-sorbitol solution or Ringer's solution on use.

EXAMPLE 6

The distilled water for injection (200 g) was placed in a one-litre beaker, to which sorbitol (300 g) was added with stirring and dissolved. At this time, if necessary the solution may be heated. Then, glycerine (200g) and ethanol (200 g) were added and mixed with stirring followed by adding argipidine (100 g) with stirring. Further, the distilled water for injection was added till the total volume of the solution became 1 litre.

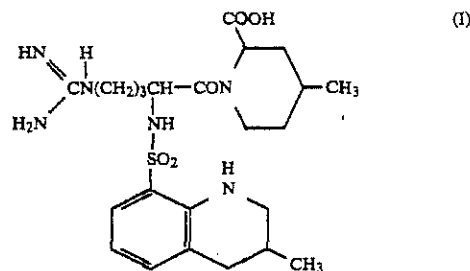
The thus-obtained solution can be used for dialyses after diluting the weak acidic solution containing D-sorbitol.

EFFECT OF THE INVENTION

According to the method for dissolving the arginineamide of the invention, the injection containing any of the arginineamides having the general formula (I) and/or their salts, particularly at high concentration can be obtained.

What is claimed is:

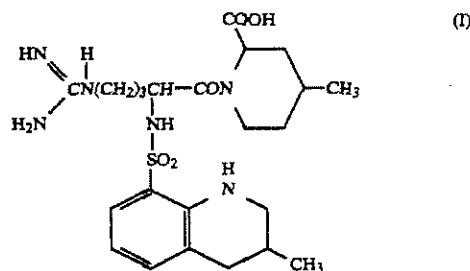
1. A method for dissolving an arginineamide, comprising:
dissolving N²-arylsulfonyl-L-argininamide represented by formula (I):



and/or its salt in a solvent containing ethanol, water and a saccharide.

2. The method according to claim 1, wherein the saccharide is at least one member selected from the group consisting of sorbitol, glucose, glycerin and sucrose.

3. A pharmaceutical composition for injection, comprising:
N²-arylsulfonyl-L-argininamide represented by formula (I):



and/or its salt together with ethanol, water and a saccharide.

4. The composition according to claim 3, wherein the saccharide is at least one member selected from the group consisting of sorbitol, glucose, glycerin and sucrose.

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